

## **REMARKS**

The Applicants thank the Examiner with much appreciation for his indication that claims 17-29 would be allowable if a terminal disclaimer is filed and if claim 17 is amended to recite: (1) hypercholesterolemia among the diseases to be treated, (2) that the liposomes are "empty," and (3) that the liposomes have a certain Gaussian distribution. In accordance with the Examiner's suggestions set forth in the Office Action and in a separate telephone conversation with Applicant's attorneys on Monday, November 17, 2003, the Applicants have canceled claim 19 and amended the claims to include the terms "hypercholesterolemia," "empty aqueous cores" and "Gaussian distribution." The term "empty aqueous cores" was used instead of "free of drug" in accordance with the Examiner's suggestion. However, the Examiner agrees that the term "empty aqueous cores" means that the aqueous cores are free of drug but does not mean that the aqueous cores are free of non-drug materials such as water and other molecules.

In addition, the Applicants submit herewith a terminal disclaimer disclaiming the terminal part of any patent granted on the above-identified application which would extend beyond the expiration date of U.S. Patent Nos. 6,312,719 and 5,746,223. During the above-mentioned telephone conversation, the Examiner also noted that he would need to confirm that the issue relating to the non-signing inventor had been resolved. For the convenience of the Examiner, the Applicants enclose a copy of the Decision Granting Status Under 37 C.F.R. § 1.47(a) showing resolution of said issue.

Claims 19, 30-43 have been canceled without prejudice. The cancellation of claim 19 was made at the Examiner's request to be consistent with amended claims 17 and 18 which now recite "having empty aqueous cores" and the cancellation of claims 30-43 were made herein for the purpose of pursuing such canceled subject matter in related applications at the option of the Applicants and not for patentability. Thus, the Applicants expressly reserve the right to prosecute any unclaimed or canceled subject matter in the present application or in any related application.

Claims 17-18 and 20-29 have been amended. Claim 17 has been amended to include the term "hypercholesterolemia" and to indicate that the liposomes have "empty aqueous cores," and to include the term "Gaussian distribution" in accordance with the Examiner's telephone suggestions. Claim 18 has been amended to be independent and claims 20-29 have been amended to indicate the proper dependency of each claim. The amended claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Specifically, the claim term "hypercholesterolemia" is supported by the specification at p. 74, *l.* 23 to p. 75, *l.* 2 and the recitation of "having empty aqueous cores" in the claims is supported by the specification at p. 24, *ll.* 12-18 (disclosing liposome [200] comprised of a phospholipid bilayer where the polar head groups [500] of the outer

leaflet face outward to the surrounding aqueous environment and the polar head groups [500] of the inner leaflet face inward to the empty aqueous core [202] of liposome particle [200]).

In addition, the term “having a Gaussian distribution wherein at least about 68% of the liposomes have a mean diameter of  $125 \pm 30$  nm” is supported by the specification at p. 78, ll. 3-11 which describes the preparation and use of a population of liposomes having a diameter of 125 nm plus or minus 30 nm as measured by QELS (Quasi-Electric-Light-Scattering) analysis, utilizing a Nicomp Model 370 submicron laser particle sizer (Pacific Scientific, MD) equipped with a 5-mW He-Ne Laser. As explained in the specification, the Nicomp QELS system used to characterize the liposome population analyzes fluctuations in light-scattering intensities due to liposome diffusion in solution. *Id.* The measured diffusion coefficient is used to obtain the average hydrodynamic radius (*see* specification at p. 78, ll. 5-6) and the mean diameter of liposomes is expressed as the mean plus or minus 1 standard deviation ( $125 \pm 30$  nm) (*see* specification at p. 78, ll. 3-11), arrived at using a Gaussian analysis (*see, The Nicomp 370 Model Submicron Particle Sizer User Manual* at pp. 24-25, entitled, “The Simplest Approach to Size Distributions: Gaussian Analysis,” previously submitted as Exhibit C in Applicant’s Reply filed on March 20, 2003).

1. **The Obviousness-Type Double Patenting Rejection Should Be Withdrawn**

The rejection under the judicially created doctrine of obvious-type double patenting should be withdrawn since the rejection is moot in view of the terminal disclaimer the Applicants have submitted herewith disclaiming the terminal part of any patent granted on the above identified application which would extend beyond the expiration date of U.S. Patent Nos. 6,312,719 and 5,746,223.

2. **The Rejection Under 35 U.S.C. §112 Second Paragraph, Should Be Withdrawn**

The Examiner rejects claims 17-33 under 35 U.S.C. § 112, second paragraph, as being indefinite because according to the Examiner, if the majority of liposomes (68%) have sizes 100-150 nm in claim 18, it is unclear how one can recite liposomes with sizes of 95-155 nm with the standard deviation recited in parent claim 17. This rejection is moot since claim 18, as amended, is now an independent claim. Accordingly, the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

3. **The Rejections Under 35 U.S.C. § 102 & 103 Should Be Withdrawn**

As stated above the Examiner has indicated that claims 17-29 would be allowable if a terminal disclaimer is filed and if the claims are amended to indicate that the

- liposomes are “empty” and the term “Gaussian distribution” is recited in the claims. The Applicants have amended the claims and filed a terminal disclaimer in accordance with the Examiner’s suggestions to put the application into condition for allowance. Accordingly, the rejections under 35 USC 102 and 103(a) are moot in view of the Applicant’s amendments and
- should be withdrawn.

### CONCLUSION

Entry of the foregoing amendments and remarks is respectfully requested. No other fee is believed to be due with this Reply. However, if any other fee is required, please charge the fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. In view of the above remarks and amendments, it is submitted that the presently pending claims are in form for allowance and early action to that end is requested. If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-9090.

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Respectfully submitted,

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